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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/000,433	11/30/2001	Kazuma Tomizuka	014643-012110US	9190

32940 7590 06/18/2003

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EXAMINER
LI, QIAN J

ART UNIT	PAPER NUMBER
1632	

DATE MAILED: 06/18/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/000,433	TOMIZUKA ET AL.	
	Examiner	Art Unit	
	Q. Janice Li	1632	

-- *The MAILING DATE of this communication appears on the cover sheet with the correspondence address* --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *31 March 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-88* is/are pending in the application.

4a) Of the above claim(s) *5 and 12-88* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-4 and 6-11* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *30 November 2001* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a)☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1)☒ Notice of References Cited (PTO-892)
2)☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3)☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4)☐ Interview Summary (PTO-413) Paper No(s). _____ .
5)☐ Notice of Informal Patent Application (PTO-152)
6)☐ Other: .

DETAILED ACTION

Election/Restrictions

Applicant's election with traverse of Group I, claims 1-11, and the species drawn to a nonhuman mammal having a the human heavy chain locus that is of a transchromosome and a human light chain locus that is associated with an endogenous mammalian chromosome, in Paper No. 7, is acknowledged. The traversal is on the ground(s) that there would be no serious burden on the Examiner to examine the claims of groups II and I together. This is not found persuasive because it is maintained that each of the Inventions requires a separate search status and consideration. The inventions are mutually exclusive and independent products drawn to mice that possess distinct genotype and phenotype, e.g. the mutation in the Fc-gamma IIB gene in a mouse genome would generate a product (group II) that require different search criteria, and different consideration assaying the impact to the genome and resulting phenotype. The searches for groups II and I would have certain overlap, but they are not co-extensive. M.P.E.P. states, "FOR PURPOSES OF THE INITIAL REQUIREMENT, A SERIOUS BURDEN ON THE EXAMINER MAY BE PRIMA FACIE SHOWN IF THE EXAMINER SHOWS BY APPROPRIATE EXPLANATION OF SEPARATE CLASSIFICATION, OR SEPARATE STATUS IN THE ART, OR A DIFFERENT FIELD OF SEARCH AS DEFINED IN MPEP § 808.02". Therefore, it is maintained that these inventions are distinct due to their divergent subject matter, and further search of these inventions is not co-extensive. The requirement is still deemed proper and is therefore made **FINAL**.

Please note that after a final requirement for restriction, the Applicants, in addition to making any response due on the remainder of the action, may petition the Commissioner to review the requirement. Petition may be deferred until after final action on or allowance of claims to the invention elected, but must be filed not later than appeal. A petition will not be considered if reconsideration of the requirement was not requested. (See § 1.181.).

Claims 1-88 are pending, however, claims 5 and 12-88 are withdrawn from further consideration by the Examiner, pursuant to 37 CFR 1.142(b), as being drawn to non-elected inventions, there being no allowable generic or linking claim. Claims 1-4, and 6-11 are under current examination.

Claim Objections

Claim 11 is objected to because of the claim recitation, "hCF(SC20)", the abbreviation should be spelled out the first time it appears in the claim.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-4 and 6-11 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for making a transgenic mouse homozygous for inactivated endogenous mu gene and kappa locus, and comprising two human

immunoglobulin loci including one heavy chain locus and a light chain locus, wherein the heavy chain locus is the SC20 fragment of human Chromosome 14 and the light chain is the KCo5 gene of human kappa light chain, does not reasonably provide enablement for making *any* transgenic non-human mammal comprising *any* human immunoglobulin loci. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

The factors to be considered when determining whether the disclosure satisfies the enablement requirements and whether undue experimentation would be required to make and use the claimed invention are summarized in *In re Wands*, (858 F2d 731, 737, 8 USPQ 2d 1400, 1404, (Fed Cir.1988)). These factors include but are not limited to the nature of the invention, the state of the prior art, the relative skill of those in the art, the predictability of the art, the breadth of the claims, and amount of direction provided. The factors most relevant to this rejection are the scope of the claims relative to the state of the art and the levels of the skilled in the art, and whether sufficient amount of direction or guidance are provided in the specification to enable one of skill in the art to practice the claimed invention.

Given the broadest reasonable interpretation, the claims encompass *any* non-human mammal ranging from rodents to primates, lacking any functional heavy and light chain loci and comprising two human Ig loci in any length and any form, e.g. inserted in the genome of the mammal or just included inside the cell in any other structural arrangement. The specification provides a transgenic mouse line comprising

two fragments of human Ig loci in working examples 1-3, and a method of making such by cross *breeding* of *a*) a transgenic hCF(SC20) mouse strain containing the fragment hCF(SC20) of the human heavy chain locus Chr14 and homozygous for inactivation mutations of the endogenous heavy chain locus (CM2D) and endogenous kappa light chain (CKD), *and b*) a transgenic KCo5-9272 mouse strain homozygous for the KCo5-9272 human transgene genome insertion and homozygous for the endogenous CMD and JKD disruptions. However, the specification fails to provide any relevant teachings or guidance with regard to production of any transgenic nonhuman mammal as claimed, whether such breeding partners are available for other mammals particularly large mammals, and the efficiency or the state of the art in making the breeding partners in other mammals, thus, fails to provide an enabling disclosure.

The physiological art in general is acknowledged to be unpredictable (MPEP 2164.03), this is particularly true in the art of transgenic animals with respect to transgene behavior. The art of transgenic animals has for many years stated that the unpredictability lies with the site or sites of integration of the transgene into the target genome. Transgenic animals are regarded to have within their cells cellular mechanisms which prevent expression of the transgene, such as DNA methylation or deletion from the genome, The elements of the particular construct used to make transgenic animals are held to be critical, and that they must be designed case by case without general rules to obtain good expression of a transgene; e.g., specific promoters, presence or absence of introns, etc. (*Houdebine* 1994, J. Biotech. 34, page 281). *Niemann* (Transg. Res. 1998, 7, page 73, col. 2, parag. 2, line 12 to page 73, col. 1, line

4)) teaches that transgenic pigs made with different promoters regulating expression of a growth hormone gene give disparate phenotypes - one deleterious to the pig, the other compatible with pig health. As the art progresses, *Logan and Sharma* (Clin Exp Pharmacol Physiol 1999 Dec;26:1020-25) teach "THE CHALLENGE IN THE DEVELOPMENT OF TRANSGENE IS NOT IN THIS PROCESS, BUT IN THE DESIGN OF THE CONSTRUCT THAT WILL ALLOW FOR THE EXPRESSION OF THE GENE OF INTEREST IN THE DESIRED CELL TYPE AT AN APPROPRIATE LEVEL", "PROBLEMS WITH OBTAINING EXPRESSION OF TRANSGENES IN AMINALS HAVE BEEN RELATED TO THE INABILITY TO ROUTINELY OBTAIN HIGH LEVELS OF EXPRESSION, ESPECIALLY OVER MULTIPLE GENERATIONS, AND THE OBSERVATION OF VARIEGATED EXPRESSION, WHEREBY NOT ALL CELLS IN AN ORGAN WILL EXPRESS THE GENE. Thus, the phenotype resulting from random insertion of any human Ig locus into the genome of any nonhuman mammal would expect to be varied and unpredictable. Without evidence to the contrary, transgene expression in different species of transgenic animals is not consistent and varies according to the particular host species. This observation is specifically supported by *Hammer et al* (J Anim Sci 1986;63:269-78), who report the production of transgenic mice, sheep and pigs; however, only transgenic mice exhibited an increase in growth due to the expression for the gene encoding human growth hormone (pages 276-277, Subsection: Effect of Foreign GH on Growth). The observation is further supported by *Mullins et al.* who report on transgenesis in the rat and larger mammals. *Mullins et al.*(J Clin Invest 1996 Apr;97:1557-60) state, "THE MAJOR PROBLEM REGARDING PRONUCLEAR MICROINJECTION IS THAT THE EXOGENOUS DNA INTEGRATES RANDOMLY INTO CHROMOSOMAL DNA. POSITION EFFECTS, WHERE THE TRANSGENE IS INFLUENCED BY ITS SIT OF INTEGRATION IN THE HOST CHROMOSOME, CAN HAVE MAJOR CONSEQUENCES ON THE EXPRESSION OF THE TRANSGENE,

INCLUDING LOSS OF CELL SPECIFICITY, INAPPROPRIATE HIGH COPY NUMBER-INDEPENDENT EXPRESSION AND COMPLETE SILENCING OF THE TRANSGENE" (paragraph bridging pages 1557-58), "THE USE OF NONMURINE SPECIES FOR TRANSGENESIS WILL CONTINUE TO REFLECT THE SUITABILITY OF A PARTICULAR SPECIES FOR THE SPECIFIC QUESTIONS BEING ADDRESSED, BEARING IN MIND THAT A GIVEN CONSTRUCT MAY REACT VERY DIFFERENTLY FROM ONE SPECIES TO ANOTHER." (page 1559, Summary). *Wall et al* (J Dairy Sci 1997;80:2213-24) report that "TRANSGENE EXPRESSION AND THE PHYSIOLOGICAL CONSEQUENCES OF TRANSGENE PRODUCTS IN LIVESTOCK ARE NOT ALWAYS PREDICTED IN TRANSGENIC MOUSE STUDIES" (page 2215, first paragraph). Further, *Sigmund* (Arteroscler. Throm. Vasc. Biol. 2000;20:1425-9, col. 1, parag. 1, lines 1-7) states that the random nature of transgene insertion, resulting founder mice can contain the transgene at a different chromosomal site, and that the position of the transgene effects expression, and thus the observed phenotype. *Linder* (Lab Animal 2001 May;30:34-9) teaches "THE GENETIC BACKGROUND AND THE SURROUNDING ENVIRONMENT ARE OFTEN OVERLOOKED PARAMETERS THAT CAN SIGNIFICANTLY AFFECT THE OBSERVED PHENOTYPE", "OTHER FACTORS INCLUDE MUTATIONS THAT ARE ACTUALLY HYPOMORPHS (I.E. MUTATIONS THAT CAUSE ONLY A PARTIAL DECREASE IN GENE EXPRESSION) RATHER THAN NULL ALLELES; COMPENSATORY PATHWAYS; AND TRANSGENESIS-SPECIFIC FACTORS, INCLUDING SITE OF INTEGRATION, TRANSGENE COPY NUMBER, AND INSERTIONAL MUTATIONS", "GENETIC BACKGROUND IS DEFINED AS A COLLECTION OF ALL GENES PRESENT IN AN ORGANISM THAT INFLUENCE A TRAIT OR TRAITS. WHILE MOST OF THE COMMONLY USED INBRED STRAINS SHARE A FAIRLY COMMON ORIGIN, EACH STRAIN HAS ITS OWN UNIQUE SET OF CHARACTERISTICS OR BACKGROUND LESIONS", "THE PHENOTYPE OF MICE CARRYING A MODIFIED GENE WILL VARY DEPENDING ON THE GENETIC BACKGROUND BECAUSE OF THE PRESENCE OF GENETIC MODIFIERS (ALLELIC VARIANTS AT LOCI

OTHER THAN THE ONE BEING GENETICALLY MODIFIED) IN THE INBRED STRAIN GENOME" (see entire article). Thus, the phenotype resulting from targeted disruption of any Ig locus in different species would expect to be varied and unpredictable. *Simerly et al* (Science 2003 Apr;300:297) states, "PRIMATE NUCLEAR TRANSFER APPEARS TO BE CHALLENGED BY STRICTER MOLECULAR REQUIREMENTS FOR MITOTIC SPINDLE ASSEMBLY THAN IN OTHER MAMMALS...WITH CURRENT APPROACHES, NT TO PRODUCE EMBRYONIC STEM CELLS IN NONHUMAN PRIMATES MAY PROVE DIFFICULT-AND REPRODUCTIVE CLONING UNACHIEVABLE". (last paragraph, page 297). Since the applicants have not disclosed any other mammal beyond the mouse, or provide sufficient guidance to do so, there is no way to predict whether the same genotype and phenotype (hCF-SC20/Kco5) could be reliably reproduced in any other mammal, particularly primates.

With regard to the stem cells used in the cloning, at the time of the effective filing date, one still cannot extrapolate results from studies generated in mice to that of primates. *Donovan and Gearhart* (Nat 2001 Nov;414:92-97) teach "HUMAN STEM CELL POPULATIONS PROLIFERATE MORE SLOWLY THAN THEIR MURINE COUNTERPARTS, DIFFERENTIATE MORE READILY AND THEIR CLONING EFFICIENCY IS VERY LOW" (last paragraph on page 95). Therefore, most of the cloning in large mammals are done in somatic cells sush as fibroblast cells. Concerning cloning from somatic cells, *Denning et al* (Nat Biotech 2001;19:559-562) teach, "A SUBSTANTIAL NUMBER OF COLONIES WITH ONLY TARGETED CELLS SENESCED BEFORE THEY COULD BE PREPARED FOR NUCLEAR TRANSFER. THE HIGH ATTRITION RATE OF TARGETED CLONAL POPULATIONS SUITABLE FOR NUCLEAR TRANSFER REPRESENTS ONE OF THE MAJOR HURDLES OF GENE TARGETING IN PRIMARY SOMATIC CELLS" (left column, page 560).

With regard to chromosomal transfer, *Green et al* (US 2003/0093820) teach, "THE TRANSCHROMOSOMES ARE MITOTICALLY AND MEIOTICALL UNSTABLE. AS A RESULT, EITHER THE HUMAN IGH, THE HUMAN IGK OR BOTH TRANSCHROMOSOMES ARE LOST WITH A FREQUENCY APPROACHING 80%" (paragraph 0012). *Tomizuka et al* (PNAS 2000 Jan;97:722-7) teach making transgenic mice with human chromosome fragments, and a previous attempt to transfer a human chromosome fragment from chromosome 14 containing *IgH* locus was failed, because the particular fragment can not be transmitted (right column, page 722). These teachings indicated that the art in chromosome transfer is still under development and highly unpredictable. Therefore, the general knowledge and levels of skill in the art do not supplement the omitted description, because specific, not general guidance is what is needed. Therefore, it is incumbent upon applicants to provide sufficient and enabling teachings within the specification for the claimed invention. Although the instant specification contemplates providing any nonhuman mammal comprising human Ig loci, it is not enabled for its full scope because based on the teaching of the specification, whether such mammal could be reproducibly made in mammals other than mouse is not predictable, and whether a mouse carrying any fragments or full length Ig loci could be reproducibly made is not predictable. One of the skill intending to practice the invention to the scope of the claims has to first carry out undue experimentation. While, the intent is not to say that transgenic animals of a particular phenotype as now broadly claimed can never be made, the intent is to provide art taught reasoning as to why the instant claims are not enabled to its scope. Given such species differences in the expression of a transgene, particularly when taken with

the lack of guidance in the specification for any transgenic non-human animal whose genome comprises any two human Ig loci , other than the exemplified transgenic mouse, it would have required undue experimentation to predict the results achieved in any host animal comprising and expressing any human Ig heavy and light chain, the levels of the transgene product, the consequences of that product, and therefore, the resulting phenotype.

Applicants are reminded that in applications directed to inventions in arts where the results are unpredictable, the disclosure of a single species usually does not provide an adequate basis to support generic claims. In re Soll, 97 F.2d 623, 38 USPQ 189 (CCPA 1938). In cases involving unpredictable factors, such as most chemical reactions and physiological activity, more may be required. In re Goodman, 29 USPQ2d 2010 (CA FC 1993); In re Fisher, 166 USPQ 18 (CCPA 1970) (contrasting mechanical and electrical elements with chemical reactions and physiological activity). See also In re Wright, 999 F.2d 1557, 27 USPQ2d 1510 (Fed. Cir. 1993); In re Vaeck, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991). This is because it is not obvious from the disclosure of one species, what other species will work. In re Dreshfield, 110 F.2d 235, 45 USPQ 36 (CCPA 1940), gives this general rule: "IT IS WELL SETTLED THAT IN CASES INVOLVING CHEMICALS AND CHEMICAL COMPOUNDS, WHICH DIFFER RADICALLY IN THEIR PROPERTIES IT MUST APPEAR IN AN APPLICANT'S SPECIFICATION EITHER BY THE ENUMERATION OF A SUFFICIENT NUMBER OF THE MEMBERS OF A GROUP OR BY OTHER APPROPRIATE LANGUAGE, THAT THE CHEMICALS OR CHEMICAL COMBINATIONS INCLUDED IN THE CLAIMS ARE CAPABLE OF ACCOMPLISHING THE DESIRED RESULT."

Furthermore, the Federal Circuit has stated that:

> a specification need not disclose what is well known in the art. See, e.g., Hybritech Inc. v. Monoclonal Antibodies, Inc., 802 F.2d 1367, 1385, 231 USPQ 81, 94 (Fed. Cir. 1986). However, that general, oft-repeated statement is merely a rule of supplementation, not a substitute for a basic enabling disclosure. It means that the omission of minor details does not cause a specification to fail to meet the enablement requirement. However, **when there is no disclosure** of any specific starting material **or of any of the conditions under which a process can be carried out, undue experimentation is required; there is a failure to meet the enablement requirement that cannot be rectified by asserting that all the disclosure related to the process is within the skill of the art.** It is the specification, not the knowledge of one skilled in the art, that must supply the novel aspects of an invention in order to constitute adequate enablement.

Genentech Inc. v. Novo Nordisk A/S, 42 USPQ2d 1005 (CAFC 1997) (emphasis added).

Considering the unpredictability in transgenic technology as taught by those skilled in the art as cited *supra*, it would have required undue experimentation for the skilled artisan intending to practice the instant invention as it is now broadly claimed.

Claim 1 recites, "a transgenic nonhuman mammal comprising two human immunoglobulin loci", which requires that at least two human chromosome fragments (loci) are present in the mammal. Claim 1 then recites, "wherein only one of said loci is of a transchromosome", and the specification defines, "*the term 'transchromosome' refers to a chromosome or fragment thereof that can be transferred into a cell of a nonhuman mammal*" (Specification, page 10. lines 7-8). However, the specification fails to teach how could one of the loci is not a chromosomal fragment, thus, fails to provide an enabling disclosure commensurate to the scope of the claims.

Claims 4 and 8 require that the human light chain locus is associated with an endogenous mammalian chromosome, wherein at least a part of the locus is cloned into a YAC vector. Assuming the "association" encompasses "integration", the YAC vector does not always integrated into the host genome, for example, as taught by *Nielsen et*

al (J Cell Biochem. 2000 Jan;76(4):674-85). The specification fails to teach how to transfer a YAC vector containing only a part of a locus into a cell, and that the YAC will be surely integrated into the endogenous genome as desired, thus, fails to provide an enabling disclosure commensurate to the scope of the claims.

Accordingly, in view of the quantity of experimentation necessary to determine the parameters for making any nonhuman mammal comprising any two of the human Ig loci, wherein only one of said loci is of a transchromosome, the lack of guidance provided by the specification as well as the absence of working examples with regard to large mammals, and the breadth of the claims, it would have required undue experimentation for one skilled in the art to make and/or use the claimed invention.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-4 and 6-11 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims are vague and indefinite because claim 1 recites, "A transgenic nonhuman mammal comprising two human immunoglobulin loci...wherein only one of said loci is of a transchromosome". The specification defines, "the term 'transchromosome' refers to a chromosome or fragment thereof that can be transferred into a cell of a nonhuman mammal" (Specification, page 10. lines 7-8). However, since a locus refers to a given gene occupies on a chromosome, "said loci" are chromosome

fragments and thus they are both "of transchromosome" based on the definition given in the specification. Accordingly, it is unclear how could only one of the loci is transchromosome and the other is not, thus, the metes and bounds of the claims are unclear.

Claims are vague and indefinite because of the claim recitation, "locus *associated* with an endogenous mammalian chromosome", the specification does not define the term, it is unclear the meaning of the term "associated" in the context of the claims, and thus the metes and bounds of the claims are unclear. For example, a human gene locus integrated into a mouse endogenous chromosome, a YAC vector carrying a Ig locus, or an independent human chromosome fragment in physical contact with a mouse endogenous chromosome can all be considered as "associated".

Claim 6 recites "the endogenous mammalian heavy chain locus". There is insufficient antecedent basis for this limitation in the claim.

Claim 6 is vague and indefinite because of the claim recitation, "at least one mammalian light chain locus". Since both the nonhuman mammal and the human subject are embraced by the term "mammalian", it is unclear which mammalian the claim intends to encompass, thus, the metes and bounds of the claim is unclear.

Claim 11 is vague and indefinite because of the claim recitation "SC20", which is a custom-term, the meaning and the content of the term is undefined in the specification, thus, the metes and bounds of the claim is unclear.

Citation of Pertinent Art

Upon clarification and/or claim amendment pertaining to the issues rejected under the first and second paragraphs of 35 U.S.C. 112, the following prior art of record may become available as prior art under *35 USC § 102 and/or 103.*

- *Fishwild et al* (Nat Biotechnol 1996;14:845-51).
- *Tomizuka et al* (Nat Genetics 1997;16:133-43).
- *Kucherlapati et al* (US 6,162,963).
- *Lonberg et al* (US 5,789,650).
- *Tomizuka et al* (PNAS 2000 Jan;97:722-7).
- *Lonberg et al* (US 5,625,126).

Conclusion

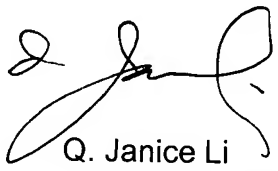
No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Q. Janice Li whose telephone number is 703-308-7942. The examiner can normally be reached on 8:30 am - 5 p.m., Monday through Friday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Deborah J. Reynolds can be reached on 703-305-4051. The fax numbers for the organization where this application or proceeding is assigned are 703-872-9306 for regular communications and 703-872-9307 for After Final communications.

Any inquiry of formal matters can be directed to the patent analyst, Dianiece Jacobs, whose telephone number is (703) 305-3388.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-1235. The faxing of such papers must conform to the notice published in the Official Gazette 1096 OG 30 (November 15, 1989).



Q. Janice Li
Patent Examiner
Art Unit 1632

QL
June 16, 2003